



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of : Heinz-Gerd KLAES) Art Unit : To be assigned  
Serial No. : 10/809,250 ) Examiner : To be assigned  
Confirmation No. : To be assigned  
Filed : March 25, 2004  
For : PHARMACEUTICAL COMPOSITION OF ANTIVIRAL  
AGENTS  
Docket No. : 1/1477

Commissioner for Patents  
Washington, D.C. 20231

CLAIM FOR FOREIGN PRIORITY UNDER 35 U.S.C. § 119

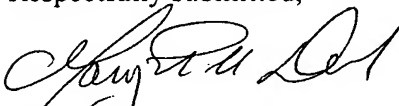
Sir:

Applicants hereby claim for the above captioned application priority of the following foreign application(s):

Foreign Priority Number:03029526.5, dated December 20, 2003, Foreign  
Priority Number 03016226.7, dated July 17, 2003 and Foreign Priority Number  
03006996.7, dated March 27, 2003.

A certified copy of the above foreign application(s) is(are) enclosed.

Respectfully submitted,

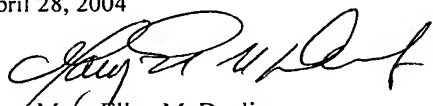
  
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By: Mary-Ellen M. Devlin  
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**Europäisches  
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Patent Office**

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**Bescheinigung**

**Certificate**

**Attestation**

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

**Patentanmeldung Nr.    Patent application No.    Demande de brevet n°**

03029526.5

Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets  
p.o.

**R C van Dijk**

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Anmeldung Nr:  
Application no.: 03029526.5  
Demande no:

Anmeldetag:  
Date of filing: 20.12.03  
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Boehringer Ingelheim International GmbH  
Binger Strasse 173  
55216 Ingelheim am Rhein  
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
Si aucun titre n'est indiqué se référer à la description.)

Pharmaceutical composition of antiviral agents

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)  
revendiquée(s)  
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/  
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of  
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL  
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What is the  $\mathbb{Z}_M$  of the twisted group?

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**Figure 1**

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**PHARMACEUTICAL COMPOSITION OF ANTIVIRAL AGENTS****FIELD OF THE INVENTION**

The present invention relates to a pharmaceutical composition  
5 useful for the treatment of viral infections comprising  
nevirapine and at least one antiviral active compound of  
formula (I). Furthermore the present invention relates to a  
use of nevirapine in combination or alternation with a  
compound of formula (I) in the prophylaxis or treatment of a  
10 viral infection in a patient. The present invention also  
relates to a use of nevirapine in combination with a compound  
of formula (I) for the manufacture of a medicament for the  
prophylaxis or treatment of a viral infection in a patient. In  
addition the present invention relates to a kit of parts and  
15 to a manufacture for the prophylaxis or treatment of a viral  
infection in a patient.

**BACKGROUND OF THE INVENTION**

20 Human immunodeficiency virus (HIV) is recognized as the  
causative agent in AIDS.

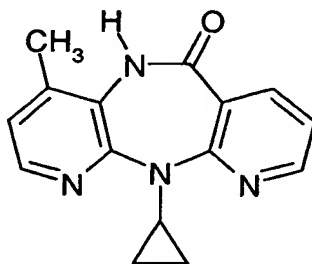
Current therapies for HIV infection focus on inhibiting the  
activity of viral enzymes which are essential to the life  
25 cycle of the virus. The agents that are presently in use fall  
mainly into three classes, designated Nucleoside Reverse  
Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse  
Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors  
(PIs). Presently, combination therapies, i.e. the selection of  
30 two or more antiretroviral agents taken together to make up a  
"drug cocktail," are the preferred treatment for HIV  
infection. Combination therapies have been shown to reduce the  
incidence of opportunistic infections and to increase survival  
time. Typically, the drug cocktail combines drugs from  
35 different classes, so as to attack the virus at several stages  
in the replication process. This approach has been shown to

- 2 -

reduce the likelihood of the development of virus forms that are resistant to a given drug or class of drugs.

5 Treatment failure with rebound of the amount of HIV which can be measured in the blood is common for patients treated with combination antiretroviral regimens. Resistance to the drugs in the drug regimen develops as the virus replicates in the presence of these drugs. Because of structural similarities of the drugs within an antiretroviral class, cross resistance is  
10 commonly seen to the other members of that class (for example virologic failure on a regimen containing an NNRTI will lead to cross resistance to the other first generation NNRTI agents). As patients experience repeated virologic failure on antiretroviral combination therapy, their viruses develop  
15 broad multi-class antiretroviral drug resistance which limits the effectiveness of the next round of antiretroviral therapy. Many highly treatment experienced patients have been exposed to all three classes of antiretroviral drugs and cannot obtain two active drugs to form the core of a new, effective  
20 antiretroviral drug regimen.

Nevirapine (Viramune®) is a non-nucleoside inhibitor of HIV reverse transcriptase, which is useful in the treatment of HIV infection in humans. The chemical name for nevirapine is  
25 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one. Its structural formula is:

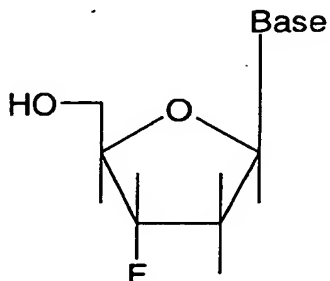


30 The earliest known synthesis of nevirapine, by Hargrave et al., is described in US Patent 5,366,972.



- 3 -

Furthermore compounds of the formula (I)



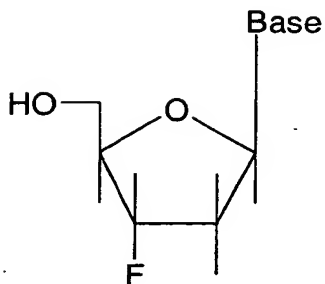
wherein Base is selected from the group consisting of thymine,  
5 cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and  
2,6-diaminopurine, or a pharmaceutically acceptable salt or  
prodrug thereof, are described in the WO 88/00050 and  
WO 91/01137 for the therapeutic and prophylactic control and  
treatment of AIDS, HIV infections, hepatitis B virus (HBV)  
10 infections and retrovirus infections in animals and man. These  
nucleoside compounds are transformed by cells or enzymes to  
triphosphates which inhibit the reverse transcriptase of  
retrovirus as well as the activity of DNA dependent polymerase  
of hepatitis B virus.

15 Combinations of nevirapine with at least one compound of the  
formula (I) which exhibit potent therapeutic activity against  
HIV and HBV would greatly aid in the development of new  
combination therapy against human retroviral (HRV) infections  
20 and HBV.

#### SUMMARY OF THE INVENTION

In one aspect, the present invention provides a novel  
pharmaceutical composition useful for the treatment or  
25 prophylaxis of viral infections comprising nevirapine and at  
least one antiviral active compound of formula (I)

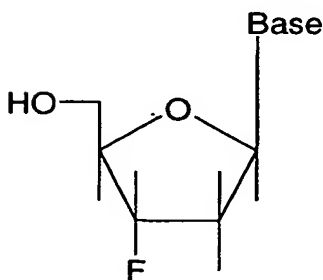
- 4 -



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or  
5 prodrug thereof.

The pharmaceutical compositions of the present invention are useful in therapy, in particular as antivirals, especially in the treatment or prophylaxis of human retroviral (HRV)  
10 infections.

In a second aspect, there is provided a use of nevirapine in combination or alternation with at least one antiviral active compound of formula (I)  
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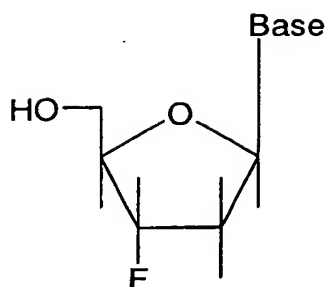


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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or  
20 prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

In a third aspect, there is provided a use of nevirapine in combination with at least one antiviral active compound of  
25 formula (I)

- 5 -

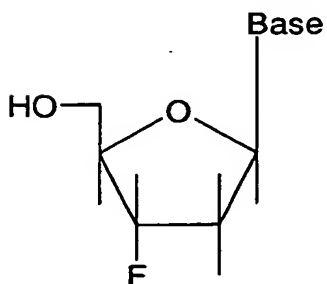


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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

In a fourth aspect of this invention, there is provided a kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising

- (a) a first containment containing a pharmaceutical composition comprising nevirapine and at least one pharmaceutically acceptable carrier, and
- (b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)

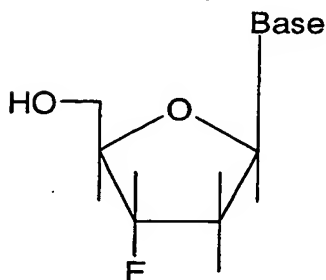


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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier.

In a fifth aspect of this invention, there is provided a manufacture comprising nevirapine and at least one antiviral active compound of formula (I)

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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or  
10 prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

With the combination of nevirapine and a compound of the formula (I) according to this invention, including its use in  
15 prophylaxis and treatment, the person skilled in the art can achieve an advantageous therapeutic effect to inhibit viral replication, especially of human retrovirus (HRV) and HBV, in particular of multiresistant HIV. In most cases, the enhanced therapeutic effect is not attainable by administration of  
20 either agent alone. In a preferred but not necessary embodiment, the effect of administration of nevirapine and the compound of formula (I) in combination or alternation is synergistic. Even though a combination exhibits additive and not synergistic effects, the combination can still provide an  
25 effect that is different from the separate administration of the two agents. For example, the biodistribution, pharmacokinetics, cytotoxic effects or metabolism of one can be affected by the other.

Further aspects of the present invention become apparent to the one skilled in the art from the following detailed description and examples.

5 **DEFINITIONS**

The term "pharmaceutically acceptable salt" means a salt of the corresponding compound which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity,  
10 irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts.  
15 Lists of suitable salts are found in, e.g., S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

As used herein, the term "treatment" means the administration  
20 of the antivirally active compounds according to this invention in combination or alternation according to the present invention to alleviate or eliminate symptoms of the viral infection and/or to reduce viral load in a patient.

25 As used herein, the term "prevention" or "prophylaxis" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms  
30 of the disease, and/or prior to the detection of the virus in the blood.

As used herein, the term "human retrovirus" (HRV) includes human immunodeficiency virus type I, human immunodeficiency  
35 virus type II, or strains thereof, as well as human T cell

leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

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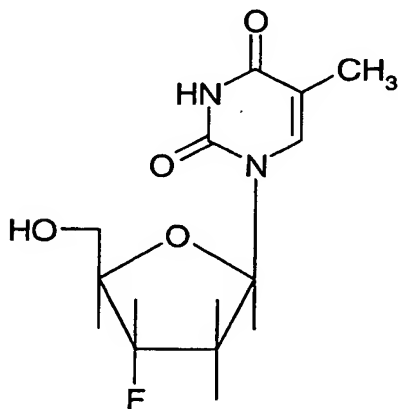
#### DETAILED DESCRIPTION OF THE INVENTION

The virally active agents according to this invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy, 10 or other reactive groups. The protecting groups may be any of those known in the art. Furthermore, the virally active agents according to this invention may also be used as in form of their pharmacologically acceptable salts and/or hydrates.

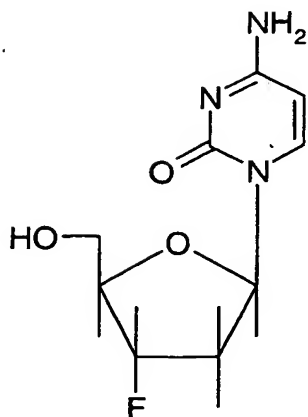
15 According to the first aspect of this invention, there is provided a novel pharmaceutical composition useful for the treatment of viral infections comprising nevirapine and at least one antiviral active compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

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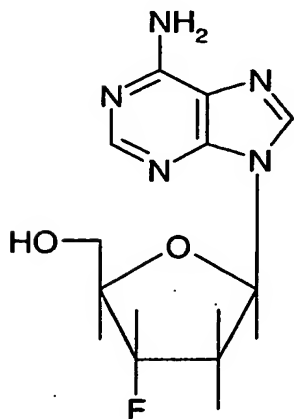
The following known compounds constitute part of the invention as preferred compounds of the formula (I) to be combined with nevirapine:



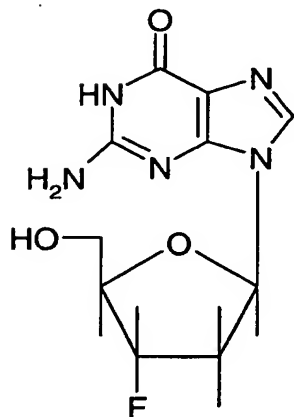
3'-deoxy-3'-fluorothymidine (FLT)



2',3'-dideoxy-3'-fluorocytidine



2',3'-dideoxy-3'fluoroadenosine



2',3'-dideoxy-3'-fluoroguanosine  
(FLG)

including pharmaceutically acceptable salts and prodrugs of the compounds listed above.

- 5 Preferred prodrugs of FLG are described in WO 99/09031 and WO 99/41268, which documents in their entirety are incorporated herein by reference.

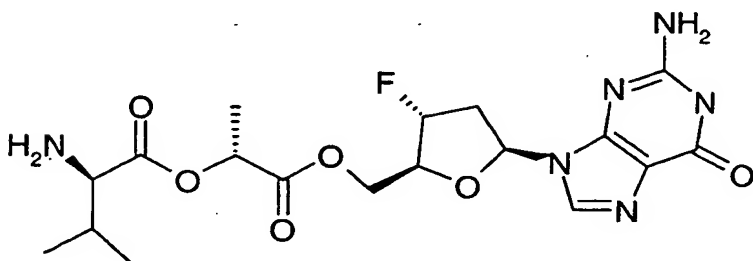
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The most preferred compound of the formula (I) to be combined with nevirapine according to the aspects of this invention is selected from the group consisting of

- (a) 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and  
(b) 2',3'-dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

The compound of the formula (I) is very most preferably selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, including pharmaceutically acceptable salts thereof.

3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine is a preferred prodrug of FLG and can be depicted by the following structure



The synthesis of 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, also named as 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, is described in the WO 99/09031 and especially in example 32 therein.

Therefore, a preferred pharmaceutical composition useful for the treatment of viral infections comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-



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valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof.

Furthermore, nevirapine in combination or alternation with  
5 preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, is used in the prophylaxis or treatment of a viral infection in a patient.

10 Also preferred is the use of nevirapine in combination with 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral  
15 infection in a patient.

A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

(a) a first containment containing a pharmaceutical  
20 composition comprising nevirapine and a pharmaceutically acceptable carrier, and  
(b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a  
25 pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

A preferred manufacture comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-  
30 propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in a patient.

The advantageous effects of the combination of nevirapine and  
35 the compound of formula (I) are realized over a wide ratio, like for example in a ratio of between 1:250 to 250:1.

Therefore, in the compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention, nevirapine and the at least one compound of formula (I), which is preferably 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, are preferably present in a synergistic ratio. Usually, this ratio is between about 1:250 to about 250:1. More preferably the ratio is between about 1:50 to about 50:1. The most preferred ratio is between about 1:20 to about 20:1, which includes the ratios 1:18, 1:16, 1:14, 1:12, 1:10; 1:8; 1:6; 1:5; 1:4; 1:3; 1:2,5; 1:2; 1:1,5; 1:1,2; 1:1; 1,2:1; 1,5:1; 2:1; 2,5:1; 3:1; 4:1; 5:1; 6:1; 8:1; 10:1, 12:1, 14:1, 16:1, 18:1 and all ranges in between. If a further therapeutic agent is added, ratios will be adjusted accordingly.

It will be appreciated that the amount of pharmaceutical composition according to the invention required for use in treatment or prophylaxis will vary not only with the particular compound selected but also with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician or veterinarian. In general however the active compounds are included in the pharmaceutically acceptable carrier in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication in vivo, especially HIV replication, without causing serious toxic effects in the treated patient. By "inhibitory amount" is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein. A suitable dose will preferably be in the range of from about 0.05 to about 200 mg/kg of body weight per day.

The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate

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intervals, for example as two, three, four or more doses per day.

5 The pharmaceutical composition according to the present invention is conveniently administered in unit dosage form; for example containing 5 to 3000 mg, conveniently 5 to 1000 mg of active ingredient(s) per unit dosage form.

10 The pharmaceutical acceptable carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Examples of pharmaceutically acceptable carriers are magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Carriers which are suited to achieve a sustained release, for  
15 example natural or synthetic polymers or liposomes, are known to the one skilled in the art. Pharmaceutically acceptable carriers also comprise liquid carriers and diluents, for example water, alcohol, glycerine or oil, which serve as a base for liquid formulations, such as solutions, suspensions  
20 or emulsions.

The compositions referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and therefore pharmaceutical formulations  
25 comprising a composition as defined above together with a pharmaceutically acceptable carrier comprise a further aspect of the invention.

30 The individual components of such compositions may be administered either in combination, i.e. simultaneously, or in alternation, i.e. sequentially, in separate or combined pharmaceutical formulations.

35 When nevirapine is used in combination with a compound of the formula (I) against the same virus the dose of each compound may be either the same as or differ from that when the

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compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

5 The compositions according to this invention preferably also comprise at least one pharmaceutically acceptable carrier.

10 According to the third aspect of this invention, the combination of nevirapine and at least one compound of the formula (I) is used for the manufacture of a medicament for the prophylaxis or the treatment of a viral infection in a patient.

15 According to one embodiment, this medicament may be a unit dosage form, which is preferably useful in combination therapy, such as capsules or tablets. The unit dosage form contains a pharmaceutical composition according to this invention, i.e. nevirapine in combination with at least one compound of the formula (I), with at least one pharmaceutically acceptable carrier.

20 Therefore, another object of this invention also comprises bringing nevirapine and at least a compound of the formula (I) together in conjunction or association with a pharmaceutically acceptable carrier.

25 According to another embodiment, this medicament is a multiple dosage form, preferably a kit of parts, which is especially useful in alternation and/or combination therapy to flexibly suit the individual therapeutic needs of the patient.

30

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According to further embodiments the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof comprise a combination selected from the group consisting of:

- 5   ▪ a compound of the formula (I), nevirapine and one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, an entry inhibitor  
10   and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease  
15   inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs.

In the above listed combinations, compositions, kit of parts, manufactures and uses thereof a protease inhibitor may  
20   advantageously be combined with ritonavir in order to improve the pharmacokinetics of said protease inhibitor.

In the foregoing and in the following, the term "further NRTI" refers to a nucleoside reverse transcriptase inhibitor, or a  
25   pharmaceutically acceptable salt or prodrug thereof, other than the selected compound of the formula (I). Examples of further NRTIs are Abacavir Sulfate (Ziagen), Didanosine (ddI, Videx), Emtricitabine (Emtriva), Lamivudine (3TC, Epivir), Stavudine (d4t, Zerit), Tenofovir disoproxil fumarate  
30   (nucleotide, bis (POC) PMPA, Viread), Zalcitabine (ddc, Hivid), Zidovudine (AZT, Retrovir), Amdoxovir (DAPD; Gilead Sciences), Elvucitabine (ACH-126443; Achillion Pharm.), GS-7340 (Gilead Sciences), INK-20 (thioether phospholipid formulation of AZT; Kucera Pharm.), MIV-310 (Medivir AB), MIV-  
35   210 (Medivir AB), Racivir (racemic FTC; Pharmasset), Reverset (RVT, D-D4FC, DPC-817; Pharmasset), SPD-754 ((-)-dOTC; Shire Pharm), BCH-13520 (Shire Pharm) and BCH-10618 (Shire Pharm).

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In the foregoing and in the following, the term "protease inhibitor" refers to a protease inhibitor, or a pharmaceutically acceptable salt or prodrug thereof. Examples  
5 of protease inhibitors are Amprenavir (VX-478, Agenerase), Atazanavir (Reyataz), Indinavir Sulfate (MK-639, Crixivan), Lexiva (fosamprenavir calcium, GW -433908 or 908, VX-175), Lopinavir + Ritonavir (ABT-378/r, Kaletra), Nelfinavir Mesylate (Viracept), Ritonavir (ABT-538, Norvir), Saquinavir  
10 (Invirase, Fortovase), Tipranavir + Ritonavir, AG-1776 (JE-2147, KNI-764; Nippon Mining Holdings), AG-1859 (Pfizer), DPC-681/684 (BMS), GS224338 ('4338; Gidead Sciences), KNI-272 (Nippon Mining Holdings), Nar-DG-35 (Narhex), P(PL)-100 (P-1946; Procyon Biopharma), P-1946 (Procyon Biopharma), R-944  
15 (Hoffmann-LaRoche), RO-0334649 (Hoffmann-LaRoche), TMC-114 (Johnson & Johnson), VX-385 (GW-640385; GSK/Vertex) and VX-478 (Vertex/GSK).

In the foregoing and in the following, the term "entry  
20 inhibitor" refers to an entry inhibitor, including fusion inhibitors, inhibitors of the CD4 receptor, inhibitors of the CCR5 co-receptor and inhibitors of the CXCR4 co-receptor, or a pharmaceutically acceptable salt or prodrug thereof. Examples of entry inhibitors are AMD-070 (AMD-11070; AnorMed),  
25 BlockAide/CR (ADVENTRX Pharm.), BMS 806 (BMS-378806; BMS), Enfuvirtide (T-20, R698, Fuzeon), KRH-1636 (Kureha Pharmaceuticals), ONO-4128 (GW-873140, AK-602, E-913; ONO Pharmaceuticals), Pro-140 (Progenics Pharm), PRO-542 (Progenics Pharm.), SCH-D (SCH-417690; Schering-Plough), T-  
30 1249 (R724; Roche/Trimeris), TAK-220 (Takeda Chem. Ind.), TNX-355 (Tanox) and UK-427,857 (Pfizer).

Examples of an integrase inhibitors are L-870810 (Merck & Co.), c-2507 (Merck & Co.) and S(RSC)-1838 (Shionogi/GSK).

35

According to still further embodiments the combinations, compositions, kit of parts, manufactures of this invention and

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the uses thereof comprise a combination selected from the group consisting of a compound of the formula (I), nevirapine and a further antiviral agent.

5 A further antiviral agent may be selected from the group of the maturation inhibitors, antisense compounds or NNRTIs, other than nevirapine. Examples of further antivirals are PA-457 (Panacos), KPC-2 (Kucera Pharm.), HGTV-43 (Enzo Biochem), Delavirdine (Rescriptor), Efavirenz (DMP-266, Sustiva), (+)-  
10 Calanolide A and B (Advanced Life Sciences), Capravirine (AG1549, S-1153; Pfizer), GW-695634 (GW-8248; GSK), MIV-150 (Medivir), MV026048 (R-1495; Medivir AB/Roche), NV-05 (Idenix Pharm.), R-278474 (Johnson & Johnson), RS-1588 (Idenix Pharm.), TMC-120/125 (Johnson & Johnson), TMC-125 (R-165335;  
15 Johnson & Johnson), UC-781 (Biosyn Inc.) and YM-215389 (Yamanouchi).

The combinations, compositions, kit of parts, manufactures of this invention and the uses thereof of the above mentioned  
20 embodiments may be combined with further active ingredients.

Examples of such further active ingredients are acyclic nucleosides such as acyclovir, ganciclovir; interferons such as alpha-, beta- and gamma-interferon; glucuronation  
25 inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, amplitgen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose,  
30 castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments, CD4-hybrid molecules and inhibitors of the HIV aspartyl protease such as L-735,524.

35 The compounds, or their pharmaceutically acceptable derivative or salts thereof, can also be mixed with other active materials that do not impair the desired action, or with

materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatorics, protease inhibitors, or other nucleoside or non-nucleoside antiviral agents, as discussed in more detail above.

5

In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on such factors as absorption, biodistribution, metabolism and excretion rates for each drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Examples of suitable dosage ranges for nevirapine, compounds of formula (I), preferably 3'-deoxy-3'-fluorothymidine, further NRTIs and other antivirals can be found in the scientific literature. Many examples of suitable dosage ranges for other compounds described herein are also found in the public literature or can be identified using known procedures. These dosage ranges can be modified as desired to achieve a desired result.

It has been recognized that drug-resistant variants of HIV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in the viral life cycle, and most typically in the case of HIV, in either the reverse transcriptase or protease genes. It has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation(s) from that selected for by the principle drug. Alternatively, the



pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. In the case of administering the antiviral compounds in alternation, i.e. sequentially, the time gap between administering the first compound and the second compound is preferably not too long in order to achieve a beneficial effect. Preferably, the time gap is less than half a day, most preferably less than 6 hours.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising nevirapine and a compound of the formula (I) with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub lingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration in liquid or solid form or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound(s) with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulation suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets

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each containing a predetermined amount of the active ingredient(s); as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active ingredient(s) may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient(s) may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently

formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and shaping in moulds.

- 5 When desired the above described formulations adapted to give sustained release of the active ingredient(s) may be employed.

10 The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention are advantageous in the treatment and/or prophylaxis of viral infections in a patient, preferably human retrovirus (HRV) infections and hepatitis B, in particular HIV infections, especially multiresistant HIV infections. Therefore this  
15 invention may offer an aid especially for highly treatment experienced patients suffering from multiresistant HIV. In addition to the treatment of said diseases, the combinations, formulations and compositions according to this invention can be used prophylactically to prevent or retard the progression  
20 of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention  
25 may also be beneficial in preventing perinatal transmission of human retroviral (HRV) infections, in particular HIV-1, from mother to baby. According to this method, nevirapine and a compound of the formula (I), preferably 3'-deoxy-3'-fluorothymidine, and optionally further active compounds as  
30 described hereinbefore or hereinafter are administered in combination or alternation to the mother before giving birth.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention  
35 may also be beneficial in the treatment and/or prophylaxis of other HIV/AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-

related neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

5 Therefore, patients to be treated would be especially those individuals:

1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum; and/or

10 2) in the case of HIV, having either a asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia, iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being  
15 less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm<sup>3</sup> in the peripheral blood.

The pharmaceutical combination according to this invention can be tested for additive and synergistic activity against HIV  
20 according to a number of assays known in scientific and public literature, including the one described in the WO 98/44913 and WO 00/51641, which are included herein by way of reference.

The present invention is illustrated in further detail by the  
25 following non-limiting examples of combinations according to this invention, comprising a 1<sup>st</sup> compound, a 2<sup>nd</sup> compound, optionally a 3<sup>rd</sup> compound, optionally a 4<sup>th</sup> compound and optionally a 5<sup>th</sup> compound.

30 Table 1 illustrating combinations of a compound of the formula (I), nevirapine and one, two or more further NRTIs

1 <sup>st</sup> compound	2 <sup>nd</sup> compound	3 <sup>rd</sup> compound
FLT	Nevirapine	Abacavir Sulfate

FLT	Nevirapine	Didanosine
FLT	Nevirapine	Emtricitabine
FLT	Nevirapine	Lamivudine
FLT	Nevirapine	Stavudine
FLT	Nevirapine	Tenofovir disoproxil fumarate
FLT	Nevirapine	Zalcitabine
FLT	Nevirapine	Zidovudine
FLT	Nevirapine	Amdoxovir
FLT	Nevirapine	Elvucitabine
FLT	Nevirapine	GS-7340
FLT	Nevirapine	INK-20
FLT	Nevirapine	MIV-210
FLT	Nevirapine	Racivir
FLT	Nevirapine	Reverset
FLT	Nevirapine	SPD-754
FLT	Nevirapine	BCH-13520
FLT	Nevirapine	BCH-10618
FLG	Nevirapine	Abacavir Sulfate
FLG	Nevirapine	Didanosine
FLG	Nevirapine	Emtricitabine
FLG	Nevirapine	Lamivudine
FLG	Nevirapine	Stavudine
FLG	Nevirapine	Tenofovir disoproxil fumarate
FLG	Nevirapine	Zalcitabine

FLG	Nevirapine	Zidovudine
FLG	Nevirapine	Amdoxovir
FLG	Nevirapine	Elvucitabine
FLG	Nevirapine	GS-7340
FLG	Nevirapine	INK-20
FLG	Nevirapine	MIV-310
FLG	Nevirapine	Racivir
FLG	Nevirapine	Reverset
FLG	Nevirapine	SPD-754
FLG	Nevirapine	BCH-13520
FLG	Nevirapine	BCH-10618

Table 2 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor and optionally one, two or more further NRTIs

5

1 <sup>st</sup> compound	2 <sup>nd</sup> compound	3 <sup>rd</sup> compound
FLT	Nevirapine	Amprenavir
FLT	Nevirapine	Atazanavir
FLT	Nevirapine	Indinavir Sulfate
FLT	Nevirapine	Lexiva
FLT	Nevirapine	Lopinavir + Ritonavir
FLT	Nevirapine	Nelfinavir Mesylate
FLT	Nevirapine	Ritonavir
FLT	Nevirapine	Saquinavir
FLT	Nevirapine	Tipranavir + Ritonavir

FLT	Nevirapine	AG-1776
FLT	Nevirapine	AG-1859
FLT	Nevirapine	DPC-681/684
FLT	Nevirapine	GS224338
FLT	Nevirapine	KNI-272
FLT	Nevirapine	Nar-DG-35
FLT	Nevirapine	P(PL)-100
FLT	Nevirapine	P-1946
FLT	Nevirapine	R-944
FLT	Nevirapine	RO-0334649
FLT	Nevirapine	TMC-114
FLT	Nevirapine	VX-385
FLT	Nevirapine	VX-478
FLG	Nevirapine	Amprenavir
FLG	Nevirapine	Atazanavir
FLG	Nevirapine	Indinavir Sulfate
FLG	Nevirapine	Lexiva
FLG	Nevirapine	Lopinavir + Ritonavir
FLG	Nevirapine	Nelfinavir Mesylate
FLG	Nevirapine	Ritonavir
FLG	Nevirapine	Saquinavir
FLG	Nevirapine	Tipranavir + Ritonavir
FLG	Nevirapine	AG-1776
FLG	Nevirapine	AG-1859

FLG	Nevirapine	DPC-681/684
FLG	Nevirapine	GS224338
FLG	Nevirapine	KNI-272
FLG	Nevirapine	Nar-DG-35
FLG	Nevirapine	P(PL)-100
FLG	Nevirapine	P-1946
FLG	Nevirapine	R-944
FLG	Nevirapine	RO-0334649
FLG	Nevirapine	TMC-114
FLG	Nevirapine	VX-385
FLG	Nevirapine	VX-478

Table 3 illustrating combinations of a compound of the formula (I), nevirapine, an entry inhibitor and optionally one, two or more further NRTIs

5

1 <sup>st</sup> compound	2 <sup>nd</sup> compound	3 <sup>rd</sup> compound
FLT	Nevirapine	Enfurvirtide
FLT	Nevirapine	T-1249
FLT	Nevirapine	AMD-070
FLT	Nevirapine	BlockAide/CR
FLT	Nevirapine	BMS 806
FLT	Nevirapine	KRH-1636
FLT	Nevirapine	ONO-4128
FLT	Nevirapine	Pro-140
FLT	Nevirapine	PRO-542
FLT	Nevirapine	SCH-D
FLT	Nevirapine	TAK-220
FLT	Nevirapine	TNX-355



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FLT	Nevirapine	UK-427,857
FLG	Nevirapine	Enfurvirtide
FLG	Nevirapine	T-1249
FLG	Nevirapine	AMD-070
FLG	Nevirapine	BlockAide/CR
FLG	Nevirapine	BMS 806
FLG	Nevirapine	KRH-1636
FLG	Nevirapine	ONO-4128
FLG	Nevirapine	Pro-140
FLG	Nevirapine	PRO-542
FLG	Nevirapine	SCH-D
FLG	Nevirapine	TAK-220
FLG	Nevirapine	TNX-355
FLG	Nevirapine	UK-427,857

Table 4 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs

5

1 <sup>st</sup> compound	2 <sup>nd</sup> compound	3 <sup>rd</sup> compound	4 <sup>th</sup> compound
FLT	Nevirapine	Amprenavir	Enfurvirtide
FLT	Nevirapine	Amprenavir	T-1249
FLT	Nevirapine	Amprenavir	AMD-070
FLT	Nevirapine	Amprenavir	BlockAide/CR
FLT	Nevirapine	Amprenavir	BMS 806
FLT	Nevirapine	Amprenavir	KRH-1636
FLT	Nevirapine	Amprenavir	ONO-4128
FLT	Nevirapine	Amprenavir	Pro-140

FLT	Nevirapine	Amprenavir	PRO-542
FLT	Nevirapine	Amprenavir	SCH-D
FLT	Nevirapine	Amprenavir	TAK-220
FLT	Nevirapine	Amprenavir	TNX-355
FLT	Nevirapine	Amprenavir	UK-427,857
FLT	Nevirapine	Atazanavir	Enfurvirtide
FLT	Nevirapine	Atazanavir	T-1249
FLT	Nevirapine	Atazanavir	AMD-070
FLT	Nevirapine	Atazanavir	BlockAide/CR
FLT	Nevirapine	Atazanavir	BMS 806
FLT	Nevirapine	Atazanavir	KRH-1636
FLT	Nevirapine	Atazanavir	ONO-4128
FLT	Nevirapine	Atazanavir	Pro-140
FLT	Nevirapine	Atazanavir	PRO-542
FLT	Nevirapine	Atazanavir	SCH-D
FLT	Nevirapine	Atazanavir	TAK-220
FLT	Nevirapine	Atazanavir	TNX-355
FLT	Nevirapine	Atazanavir	UK-427,857
FLT	Nevirapine	Indinavir Sulfate	Enfurvirtide
FLT	Nevirapine	Indinavir Sulfate	T-1249
FLT	Nevirapine	Indinavir Sulfate	AMD-070
FLT	Nevirapine	Indinavir Sulfate	BlockAide/CR
FLT	Nevirapine	Indinavir Sulfate	BMS 806

FLT	Nevirapine	Indinavir Sulfate	KRH-1636
FLT	Nevirapine	Indinavir Sulfate	ONO-4128
FLT	Nevirapine	Indinavir Sulfate	Pro-140
FLT	Nevirapine	Indinavir Sulfate	PRO-542
FLT	Nevirapine	Indinavir Sulfate	SCH-D
FLT	Nevirapine	Indinavir Sulfate	TAK-220
FLT	Nevirapine	Indinavir Sulfate	TNX-355
FLT	Nevirapine	Indinavir Sulfate	UK-427,857
FLT	Nevirapine	Lexiva	Enfurvirtide
FLT	Nevirapine	Lexiva	T-1249
FLT	Nevirapine	Lexiva	AMD-070
FLT	Nevirapine	Lexiva	BlockAide/CR
FLT	Nevirapine	Lexiva	BMS 806
FLT	Nevirapine	Lexiva	KRH-1636
FLT	Nevirapine	Lexiva	ONO-4128
FLT	Nevirapine	Lexiva	Pro-140
FLT	Nevirapine	Lexiva	PRO-542
FLT	Nevirapine	Lexiva	SCH-D
FLT	Nevirapine	Lexiva	TAK-220
FLT	Nevirapine	Lexiva	TNX-355
FLT	Nevirapine	Lexiva	UK-427,857

FLT	Nevirapine	Lopinavir + Ritonavir	Enfurvirtide
FLT	Nevirapine	Lopinavir + Ritonavir	T-1249
FLT	Nevirapine	Lopinavir + Ritonavir	AMD-070
FLT	Nevirapine	Lopinavir + Ritonavir	BlockAide/CR
FLT	Nevirapine	Lopinavir + Ritonavir	BMS 806
FLT	Nevirapine	Lopinavir + Ritonavir	KRH-1636
FLT	Nevirapine	Lopinavir + Ritonavir	ONO-4128
FLT	Nevirapine	Lopinavir + Ritonavir	Pro-140
FLT	Nevirapine	Lopinavir + Ritonavir	PRO-542
FLT	Nevirapine	Lopinavir + Ritonavir	SCH-D
FLT	Nevirapine	Lopinavir + Ritonavir	TAK-220
FLT	Nevirapine	Lopinavir + Ritonavir	TNX-355
FLT	Nevirapine	Lopinavir + Ritonavir	UK-427,857
FLT	Nevirapine	Nelfinavir Mesylate	Enfurvirtide
FLT	Nevirapine	Nelfinavir Mesylate	T-1249
FLT	Nevirapine	Nelfinavir	AMD-070

		Mesylate	
FLT	Nevirapine	Nelfinavir Mesylate	BlockAide/CR
FLT	Nevirapine	Nelfinavir Mesylate	BMS 806
FLT	Nevirapine	Nelfinavir Mesylate	KRH-1636
FLT	Nevirapine	Nelfinavir Mesylate	ONO-4128
FLT	Nevirapine	Nelfinavir Mesylate	Pro-140
FLT	Nevirapine	Nelfinavir Mesylate	PRO-542
FLT	Nevirapine	Nelfinavir Mesylate	SCH-D
FLT	Nevirapine	Nelfinavir Mesylate	TAK-220
FLT	Nevirapine	Nelfinavir Mesylate	TNX-355
FLT	Nevirapine	Nelfinavir Mesylate	UK-427,857
FLT	Nevirapine	Ritonavir	Enfurvirtide
FLT	Nevirapine	Ritonavir	T-1249
FLT	Nevirapine	Ritonavir	AMD-070
FLT	Nevirapine	Ritonavir	BlockAide/CR
FLT	Nevirapine	Ritonavir	BMS 806
FLT	Nevirapine	Ritonavir	KRH-1636
FLT	Nevirapine	Ritonavir	ONO-4128
FLT	Nevirapine	Ritonavir	Pro-140
FLT	Nevirapine	Ritonavir	PRO-542

FLT	Nevirapine	Ritonavir	SCH-D
FLT	Nevirapine	Ritonavir	TAK-220
FLT	Nevirapine	Ritonavir	TNX-355
FLT	Nevirapine	Ritonavir	UK-427,857
FLT	Nevirapine	Saquinavir	Enfurvirtide
FLT	Nevirapine	Saquinavir	T-1249
FLT	Nevirapine	Saquinavir	AMD-070
FLT	Nevirapine	Saquinavir	BlockAide/CR
FLT	Nevirapine	Saquinavir	BMS 806
FLT	Nevirapine	Saquinavir	KRH-1636
FLT	Nevirapine	Saquinavir	ONO-4128
FLT	Nevirapine	Saquinavir	Pro-140
FLT	Nevirapine	Saquinavir	PRO-542
FLT	Nevirapine	Saquinavir	SCH-D
FLT	Nevirapine	Saquinavir	TAK-220
FLT	Nevirapine	Saquinavir	TNX-355
FLT	Nevirapine	Saquinavir	UK-427,857
FLT	Nevirapine	Tipranavir + Ritonavir	Enfurvirtide
FLT	Nevirapine	Tipranavir + Ritonavir	T-1249
FLT	Nevirapine	Tipranavir + Ritonavir	AMD-070
FLT	Nevirapine	Tipranavir + Ritonavir	BlockAide/CR
FLT	Nevirapine	Tipranavir + Ritonavir	BMS 806
FLT	Nevirapine	Tipranavir + Ritonavir	KRH-1636

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FLT	Nevirapine	Tipranavir + Ritonavir	ONO-4128
FLT	Nevirapine	Tipranavir + Ritonavir	Pro-140
FLT	Nevirapine	Tipranavir + Ritonavir	PRO-542
FLT	Nevirapine	Tipranavir + Ritonavir	SCH-D
FLT	Nevirapine	Tipranavir + Ritonavir	TAK-220
FLT	Nevirapine	Tipranavir + Ritonavir	TNX-355
FLT	Nevirapine	Tipranavir + Ritonavir	UK-427,857
FLG	Nevirapine	Amprenavir	Enfurvirtide
FLG	Nevirapine	Amprenavir	T-1249
FLG	Nevirapine	Amprenavir	AMD-070
FLG	Nevirapine	Amprenavir	BlockAide/CR
FLG	Nevirapine	Amprenavir	BMS 806
FLG	Nevirapine	Amprenavir	KRH-1636
FLG	Nevirapine	Amprenavir	ONO-4128
FLG	Nevirapine	Amprenavir	Pro-140
FLG	Nevirapine	Amprenavir	PRO-542
FLG	Nevirapine	Amprenavir	SCH-D
FLG	Nevirapine	Amprenavir	TAK-220
FLG	Nevirapine	Amprenavir	TNX-355
FLG	Nevirapine	Amprenavir	UK-427,857
FLG	Nevirapine	Atazanavir	Enfurvirtide
FLG	Nevirapine	Atazanavir	T-1249

FLG	Nevirapine	Atazanavir	AMD-070
FLG	Nevirapine	Atazanavir	BlockAide/CR
FLG	Nevirapine	Atazanavir	BMS 806
FLG	Nevirapine	Atazanavir	KRH-1636
FLG	Nevirapine	Atazanavir	ONO-4128
FLG	Nevirapine	Atazanavir	Pro-140
FLG	Nevirapine	Atazanavir	PRO-542
FLG	Nevirapine	Atazanavir	SCH-D
FLG	Nevirapine	Atazanavir	TAK-220
FLG	Nevirapine	Atazanavir	TNX-355
FLG	Nevirapine	Atazanavir	UK-427,857
FLG	Nevirapine	Indinavir Sulfate	Enfurvirtide
FLG	Nevirapine	Indinavir Sulfate	T-1249
FLG	Nevirapine	Indinavir Sulfate	AMD-070
FLG	Nevirapine	Indinavir Sulfate	BlockAide/CR
FLG	Nevirapine	Indinavir Sulfate	BMS 806
FLG	Nevirapine	Indinavir Sulfate	KRH-1636
FLG	Nevirapine	Indinavir Sulfate	ONO-4128
FLG	Nevirapine	Indinavir Sulfate	Pro-140
FLG	Nevirapine	Indinavir Sulfate	PRO-542



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FLG	Nevirapine	Indinavir Sulfate	SCH-D
FLG	Nevirapine	Indinavir Sulfate	TAK-220
FLG	Nevirapine	Indinavir Sulfate	TNX-355
FLG	Nevirapine	Indinavir Sulfate	UK-427,857
FLG	Nevirapine	Lexiva	Enfurvirtide
FLG	Nevirapine	Lexiva	T-1249
FLG	Nevirapine	Lexiva	AMD-070
FLG	Nevirapine	Lexiva	BlockAide/CR
FLG	Nevirapine	Lexiva	BMS 806
FLG	Nevirapine	Lexiva	KRH-1636
FLG	Nevirapine	Lexiva	ONO-4128
FLG	Nevirapine	Lexiva	Pro-140
FLG	Nevirapine	Lexiva	PRO-542
FLG	Nevirapine	Lexiva	SCH-D
FLG	Nevirapine	Lexiva	TAK-220
FLG	Nevirapine	Lexiva	TNX-355
FLG	Nevirapine	Lexiva	UK-427,857
FLG	Nevirapine	Lopinavir + Ritonavir	Enfurvirtide
FLG	Nevirapine	Lopinavir + Ritonavir	T-1249
FLG	Nevirapine	Lopinavir + Ritonavir	AMD-070
FLG	Nevirapine	Lopinavir + Ritonavir	BlockAide/CR

FLG	Nevirapine	Lopinavir + Ritonavir	BMS 806
FLG	Nevirapine	Lopinavir + Ritonavir	KRH-1636
FLG	Nevirapine	Lopinavir + Ritonavir	ONO-4128
FLG	Nevirapine	Lopinavir + Ritonavir	Pro-140
FLG	Nevirapine	Lopinavir + Ritonavir	PRO-542
FLG	Nevirapine	Lopinavir + Ritonavir	SCH-D
FLG	Nevirapine	Lopinavir + Ritonavir	TAK-220
FLG	Nevirapine	Lopinavir + Ritonavir	TNX-355
FLG	Nevirapine	Lopinavir + Ritonavir	UK-427,857
FLG	Nevirapine	Nelfinavir Mesylate	Enfurvirtide
FLG	Nevirapine	Nelfinavir Mesylate	T-1249
FLG	Nevirapine	Nelfinavir Mesylate	AMD-070
FLG	Nevirapine	Nelfinavir Mesylate	BlockAide/CR
FLG	Nevirapine	Nelfinavir Mesylate	BMS 806
FLG	Nevirapine	Nelfinavir Mesylate	KRH-1636
FLG	Nevirapine	Nelfinavir	ONO-4128

		Mesylate	
FLG	Nevirapine	Nelfinavir Mesylate	Pro-140
FLG	Nevirapine	Nelfinavir Mesylate	PRO-542
FLG	Nevirapine	Nelfinavir Mesylate	SCH-D
FLG	Nevirapine	Nelfinavir Mesylate	TAK-220
FLG	Nevirapine	Nelfinavir Mesylate	TNX-355
FLG	Nevirapine	Nelfinavir Mesylate	UK-427,857
FLG	Nevirapine	Ritonavir	Enfurvirtide
FLG	Nevirapine	Ritonavir	T-1249
FLG	Nevirapine	Ritonavir	AMD-070
FLG	Nevirapine	Ritonavir	BlockAide/CR
FLG	Nevirapine	Ritonavir	BMS 806
FLG	Nevirapine	Ritonavir	KRH-1636
FLG	Nevirapine	Ritonavir	ONO-4128
FLG	Nevirapine	Ritonavir	Pro-140
FLG	Nevirapine	Ritonavir	PRO-542
FLG	Nevirapine	Ritonavir	SCH-D
FLG	Nevirapine	Ritonavir	TAK-220
FLG	Nevirapine	Ritonavir	TNX-355
FLG	Nevirapine	Ritonavir	UK-427,857
FLG	Nevirapine	Saquinavir	Enfurvirtide
FLG	Nevirapine	Saquinavir	T-1249
FLG	Nevirapine	Saquinavir	AMD-070

FLG	Nevirapine	Saquinavir	BlockAide/CR
FLG	Nevirapine	Saquinavir	BMS 806
FLG	Nevirapine	Saquinavir	KRH-1636
FLG	Nevirapine	Saquinavir	ONO-4128
FLG	Nevirapine	Saquinavir	Pro-140
FLG	Nevirapine	Saquinavir	PRO-542
FLG	Nevirapine	Saquinavir	SCH-D
FLG	Nevirapine	Saquinavir	TAK-220
FLG	Nevirapine	Saquinavir	TNX-355
FLG	Nevirapine	Saquinavir	UK-427,857
FLG	Nevirapine	Tipranavir + Ritonavir	Enfurvirtide
FLG	Nevirapine	Tipranavir + Ritonavir	T-1249
FLG	Nevirapine	Tipranavir + Ritonavir	AMD-070
FLG	Nevirapine	Tipranavir + Ritonavir	BlockAide/CR
FLG	Nevirapine	Tipranavir + Ritonavir	BMS 806
FLG	Nevirapine	Tipranavir + Ritonavir	KRH-1636
FLG	Nevirapine	Tipranavir + Ritonavir	ONO-4128
FLG	Nevirapine	Tipranavir + Ritonavir	Pro-140
FLG	Nevirapine	Tipranavir + Ritonavir	PRO-542
FLG	Nevirapine	Tipranavir + Ritonavir	SCH-D

FLG	Nevirapine	Tipranavir + Ritonavir	TAK-220
FLG	Nevirapine	Tipranavir + Ritonavir	TNX-355
FLG	Nevirapine	Tipranavir + Ritonavir	UK-427,857

Table 5 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs

5

1 <sup>st</sup> compound	2 <sup>nd</sup> compound	3 <sup>rd</sup> compound	4 <sup>th</sup> compound
FLT	Nevirapine	Amprenavir	L-870810
FLT	Nevirapine	Amprenavir	c-2507
FLT	Nevirapine	Amprenavir	S(RSC)-1838
FLT	Nevirapine	Atazanavir	L-870810
FLT	Nevirapine	Atazanavir	c-2507
FLT	Nevirapine	Atazanavir	S(RSC)-1838
FLT	Nevirapine	Indinavir Sulfate	c-2507
FLT	Nevirapine	Indinavir Sulfate	S(RSC)-1838
FLT	Nevirapine	Indinavir Sulfate	L-870810
FLT	Nevirapine	Lexiva	c-2507
FLT	Nevirapine	Lexiva	L-870810
FLT	Nevirapine	Lexiva	S(RSC)-1838
FLT	Nevirapine	Lopinavir + Ritonavir	L-870810

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FLT	Nevirapine	Lopinavir + Ritonavir	c-2507
FLT	Nevirapine	Lopinavir + Ritonavir	S(RSC)-1838
FLT	Nevirapine	Nelfinavir Mesylate	L-870810
FLT	Nevirapine	Nelfinavir Mesylate	c-2507
FLT	Nevirapine	Nelfinavir Mesylate	S(RSC)-1838
FLT	Nevirapine	Ritonavir	L-870810
FLT	Nevirapine	Ritonavir	c-2507
FLT	Nevirapine	Ritonavir	S(RSC)-1838
FLT	Nevirapine	Saquinavir	L-870810
FLT	Nevirapine	Saquinavir	c-2507
FLT	Nevirapine	Saquinavir	S(RSC)-1838
FLT	Nevirapine	Tipranavir + Ritonavir	L-870810
FLT	Nevirapine	Tipranavir + Ritonavir	c-2507
FLT	Nevirapine	Tipranavir + Ritonavir	S(RSC)-1838
FLG	Nevirapine	Amprenavir	L-870810
FLG	Nevirapine	Amprenavir	c-2507
FLG	Nevirapine	Amprenavir	S(RSC)-1838
FLG	Nevirapine	Atazanavir	L-870810
FLG	Nevirapine	Atazanavir	c-2507
FLG	Nevirapine	Atazanavir	S(RSC)-1838
FLG	Nevirapine	Indinavir	c-2507

		Sulfate	
FLG	Nevirapine	Indinavir Sulfate	S(RSC)-1838
FLG	Nevirapine	Indinavir Sulfate	L-870810
FLG	Nevirapine	Lexiva	c-2507
FLG	Nevirapine	Lexiva	L-870810
FLG	Nevirapine	Lexiva	S(RSC)-1838
FLG	Nevirapine	Lopinavir + Ritonavir	L-870810
FLG	Nevirapine	Lopinavir + Ritonavir	c-2507
FLG	Nevirapine	Lopinavir + Ritonavir	S(RSC)-1838
FLG	Nevirapine	Nelfinavir Mesylate	L-870810
FLG	Nevirapine	Nelfinavir Mesylate	c-2507
FLG	Nevirapine	Nelfinavir Mesylate	S(RSC)-1838
FLG	Nevirapine	Ritonavir	L-870810
FLG	Nevirapine	Ritonavir	c-2507
FLG	Nevirapine	Ritonavir	S(RSC)-1838
FLG	Nevirapine	Saquinavir	L-870810
FLG	Nevirapine	Saquinavir	c-2507
FLG	Nevirapine	Saquinavir	S(RSC)-1838
FLG	Nevirapine	Tipranavir + Ritonavir	L-870810
FLG	Nevirapine	Tipranavir	c-2507

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		+ Ritonavir	
FLG	Nevirapine	Tipranavir + Ritonavir	S(RSC)-1838

Table 6 illustrating combinations of a compound of the formula (I), nevirapine and a further antiviral

1 <sup>st</sup> compound	2 <sup>nd</sup> compound	3 <sup>rd</sup> compound	4 <sup>th</sup> compound
FLT	Nevirapine	PA-457	
FLT	Nevirapine	KPC-2	
FLT	Nevirapine	HGTV-43	
FLT	Nevirapine	Delavirdine	
FLT	Nevirapine	Efavirenz	
FLT	Nevirapine	(+)- Calanolide A or B	
FLT	Nevirapine	Capravirine	
FLT	Nevirapine	GW-695634	
FLT	Nevirapine	MIV-150	
FLT	Nevirapine	MV026048	
FLT	Nevirapine	NV-05	
FLT	Nevirapine	R-278474	
FLT	Nevirapine	RS-1588	
FLT	Nevirapine	TMC-120/125	
FLT	Nevirapine	TMC-125	
FLT	Nevirapine	UC-781	
FLT	Nevirapine	YM-215389	
FLG	Nevirapine	PA-457	



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FLG	Nevirapine	KPC-2	
FLG	Nevirapine	HGTV-43	
FLG	Nevirapine	Delavirdine	
FLG	Nevirapine	Efavirenz	
FLG	Nevirapine	(+)- Calanolide A or B	
FLG	Nevirapine	Capravirine	
FLG	Nevirapine	GW-695634	
FLG	Nevirapine	MIV-150	
FLG	Nevirapine	MV026048	
FLG	Nevirapine	NV-05	
FLG	Nevirapine	R-278474	
FLG	Nevirapine	RS-1588	
FLG	Nevirapine	TMC-120/125	
FLG	Nevirapine	TMC-125	
FLG	Nevirapine	UC-781	
FLG	Nevirapine	YM-215389	

In the above given Tables 1 to 6 the term "FLG" is 2',3'-  
dideoxy-3'-fluoroguanosine, or a pharmaceutically acceptable  
salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-  
5 [2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically  
acceptable salt thereof.



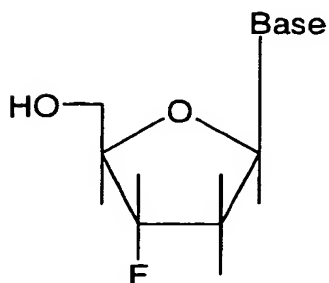
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**Claims:**

1. A pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)

5



I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

10

2. The pharmaceutical composition according to claim 1 wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

15

3. The pharmaceutical composition according to claim 1 wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

20

4. The pharmaceutical composition according to one or more of the claims 1 to 3 wherein nevirapine and the at least one compound of formula (I) are present in a synergistic ratio.

25

5. The pharmaceutical composition according to one or more of the claims 1 to 4 wherein nevirapine and the at least one compound of the formula (I) are present in a

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ratio between about 1:250 to about 250:1.

6. The pharmaceutical composition according to claim 5 wherein nevirapine and the at least one compound of the formula (I) are present in a ratio between about 1:50 to about 50:1.

7. The pharmaceutical composition according to one or more of the claims 1 to 6 further comprising one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

8. The pharmaceutical composition according to claim 7 wherein (a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

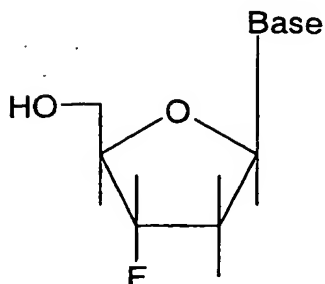
(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

9. The pharmaceutical composition according to one or more of the claims 1 to 8 with at least one pharmaceutically acceptable carrier.

10. The pharmaceutical composition according to one or more of the claims 1 to 9 for use in the treatment or prophylaxis of human retroviral (HRV) infections.

11. Use of nevirapine in combination or alternation with at least one antiviral active compound of formula (I)

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I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or  
5 prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

12. The use according to claim 11, wherein the compound of  
10 formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

13. The use according to claim 11, wherein the compound of the  
15 formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

14. The use according to claim 11, 12 or 13 in the prophylaxis  
20 or treatment of a human retroviral infection (HRV) in a patient.

15. The use according to one or more of the claims 11 or 14 in  
the prophylaxis or treatment of a multiresistant HIV infection in a patient.

16. The use according to one or more of the claims 11 to 15  
for preventing perinatal transmission of a human retroviral (HRV) infection from mother to baby.

17. The use according to one or more of the claims 11 to 16, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a synergistic ratio.

5

18. The use according to one or more of the claims 11 to 17, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a ratio between about 1:250 to about 250:1.

10

19. The use according to claim 18, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a ratio between about 1:50 to about 50:1.

15

20. The use according to one or more of the claims 11 to 19 in combination or alternation with one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

20

21. The use according to claim 20 wherein

(a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

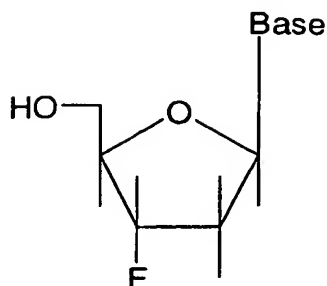
25

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

30

22. Use of nevirapine in combination with at least one antiviral active compound of formula (I)

35



I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or  
5 prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

23. The use according to claim 22, wherein the compound of  
formula (I) is 3'-deoxy-3'-fluorothymidine, or a  
10 pharmaceutically acceptable salt or prodrug thereof.

24. The use according to claim 22, wherein the compound of the  
formula (I) is FLG or a pharmaceutically acceptable salt or  
prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-  
15 valyloxy)-propionyl]guanosine or a pharmaceutically acceptable  
salt thereof.

25. The use according to claim 22, 23 or 24, wherein  
nevirapine is used in combination with said compound of the  
20 formula (I) and one, two or more further NRTI, or a  
pharmaceutically acceptable salt or prodrug thereof.

26. The use according to claim 25 wherein  
(a) the compound of the formula (I) is 3'-deoxy-3'-  
25 fluorothymidine, or a pharmaceutically acceptable salt or  
prodrug thereof, and the further NRTI is FLG or a  
pharmaceutically acceptable salt or prodrug thereof, in  
particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-  
propionyl]guanosine or a pharmaceutically acceptable salt  
30 thereof, or

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

5

27. The use according to one or more of the claims 22 to 26 for the manufacture of a medicament for the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

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28. The use according to one or more of the claims 22 to 27, wherein the medicament is a single dosage form.

29. The use according to one or more of the claim 22 to 27, wherein the medicament is a multiple dosage form.

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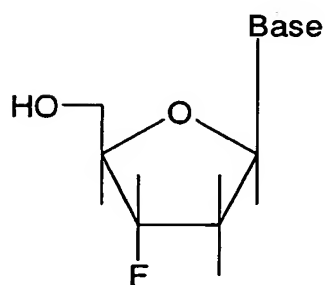
30. A kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising

(a) a first containment containing a pharmaceutical composition comprising nevirapine and at least one

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pharmaceutically acceptable carrier, and

(b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)



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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable

30

carrier.



31. The kit of parts according to claim 30, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

5

32. The kit of parts according to claim 30, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

10

33. The kit of parts according to claim 30, 31 or 32 for use in the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

15

34. The kit of parts according to one or more of the claim 30 to 33 further comprising one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

20

35. The kit of parts according to claim 34 wherein (a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

25

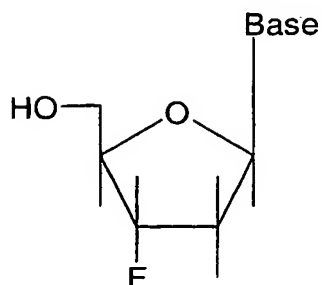
(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

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36. A manufacture comprising nevirapine and at least one antiviral active compound of formula (I)

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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or  
5 prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

37. The manufacture according to claim 36, wherein the  
10 compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

38. The manufacture according to claim 36, wherein the compound  
15 of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

39. The manufacture according to claim 36, 37 or 38 for use in  
20 combination or alternation in the prophylaxis or treatment of a human retroviral (HRV) infection in patient.

40. The manufacture according to one or more of the claims 36  
25 to 39 further comprising one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

41. The manufacture according to claim 40 wherein  
30 (a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in

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particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-  
propionyl]guanosine or a pharmaceutically acceptable salt  
thereof, or

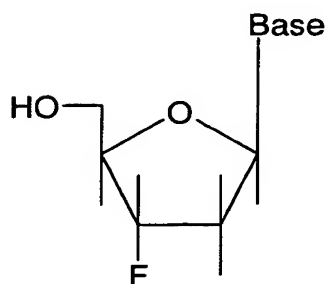
- (b) the compound of the formula (I) is FLG or a  
5 pharmaceutically acceptable salt or prodrug thereof, and the  
further NRTI is 3'-deoxy-3'-fluorothymidine, or a  
pharmaceutically acceptable salt or prodrug thereof.



20. Dez. 2003

**Summary**

In accordance with the present invention there is provided a pharmaceutical composition useful for the treatment or  
5 prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)



I

wherein Base is selected from the group consisting of thymine,  
10 cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

